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Pabst Patent Group LLP
1545 PEACHTREE STREET NE
SUITE 320
ATLANTA, GA 30309

EXAMINER	
FUBARA, BLESSING M	

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/053,929
Filing Date: January 22, 2002
Appellant(s): STRAUB ET AL.

Michael J. Terapane
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 07/09/07 appealing from the Office action mailed 12/08/2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Unger, van C. "Solid Matrix Therapeutic Compositions" United States Patent Application Publication, Pub. No. US 2001/0018072 (Aug 30, 2001).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16-21 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger (US 2001/0018072).

Unger discloses solid porous matrix that contains bioactive agent, surfactant and solvent (abstract) and a bicarbonate (paragraph 167); the solvent can be organic or aqueous (paragraph 74); the drying methods include, lyophilizing, spray drying, and the combination thereof (paragraphs 14 and 76); some of the bioactive agents that can be prepared according to Unger are anti-neoplastic agents, methotrexate, adriamycin (paragraph 135). Surfactant is an excipient. Ammonium carbonate is a volatile pore forming salt. The instant method comprises steps a-d and the steps a-c read on mixing the bioactive agent, the volatile pore forming agent and excipient and removes the solvent by lyophilizing or spray drying. The lyophilizing step in Unger is a process of removing solvent and the pore forming agent as is claim 16 d. Unger's method steps may not specifically disclose the claimed method steps according to the steps from 16 a-d. For example, in example 1, Unger places dexamethasone in PEG and that mixture is then dissolved in methanol and rotary evaporated under vacuum. There is no demonstration that the recited method steps, in the exact order provides unexpected results to the porous matrix and

also that the specific method steps are known in the art for the production of powder formulation (for example, column 2, lines 49-51; column 3, line 30 and column 9, line 41, of US 5,976,574 issued to Gordon, Nov. 02, 1999 a teaching reference, discloses preparing powder by dissolving a drug in the solvent, adding excipient to the solution and then spray drying). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a porous matrix according to Unger. One having ordinary skill in the art would have been motivated to use the known steps of preparing the powder with the expectation of forming a porous matrix. In the absence of showing factual evidence, the recited steps of making the porous matrix does not patentably distinguish the claimed invention over the prior art.

(10) Response to Argument

a) Appellant says that Unger does not disclose or suggest elements (a), (b), (c), and (d) of claims 16, that describes a method for preparing solid porous matrix by combining surfactant and therapeutic with a solvent to form an emulsion containing random aggregates of the surfactant and the therapeutic and processing the emulsion to form the matrix, that the solvent in Unger is a suspending medium for the surfactant and therapeutic and that the therapeutic is only marginally soluble in the solvent and that in contrast, the active agent is dissolved in the volatile solvent to form a drug solution and that a suspension is not a solution.

The examiner agrees with the appellant that Unger does not teach the method in the sequence claimed and that is why the rejection is under 35 USC 103, it is noted that selection of any order performing process steps or mixing ingredients is prima facie obvious in the absence of new and unexpected results. Appellant acknowledges that the order of the process of preparing the porous matrix in Unger is not the same as that claimed but has failed to provide

new and unexpected results derived from the claimed sequence of mixing the ingredients. Regarding the appellant's argument that Unger forms a suspension as opposed to a solution according to step (a) of claim 16, it is noted that the goal of the process is the formation of a porous matrix and the end result of Unger's process is that a porous matrix is prepared, secondly, Unger discloses that the drug is solubilized by the presence of oil in the composition (see paragraph [0184]), and in all, Appellant is arguing against the sequence of the steps without providing factual showing that the claimed sequence provides unexpected results. It is also noted that that step 6 (b) forms an emulsion or suspension; and as it regards the solvent, the claim recites organic solvent and Unger states that the solvent can be organic, such that while appellant's statement that the solvent in Unger is a suspending agent for the therapeutic and surfactant may be true and supported by the disclosure of Unger, it is also true that suspending capacity of the solvent for the therapeutic agent and the surfactant is derived from the properties of the solvent. Thus, since the appealed claim broadly refers to organic solvent, and the Unger disclosure contemplates the use of organic solvent, it flows that when the properties of organic solvents are considered, the organic solvent in both the appealed claims and Unger should display the same effects and characteristics. However, appellant has not shown the difference between the solvent of Unger and the solvent of the claims keeping in mind that organic solvent in claim 16 is generic encompassing any and all organic solvent.

a2) Appellant also argues that Unger teaches away from the claimed method because one of ordinary skill in the art would be led by the teaching of Unger to prepare a suspension or emulsion of the active agent and not a solution. The examiner disagrees because i) the purpose or goal of claim 16 is to prepare composition comprising porous matrix formed of at least one

hydrophilic or hydrophobic excipient and microparticles of a drug, all generic. Unger teaches the preparation of porous matrix comprising drug particles and surfactants that meet the requirements for hydrophobic or hydrophilic excipients, the use of ammonium carbonate meets the volatile solid pore forming agent, and because the process of Unger, though not the exact sequence of claim 16, produces porous matrix as described above would guide the artisan to prepare a porous matrix. Regarding the solution of the active agent in the organic solvent, it is noted that Unger specifically suggests that the therapeutic agent is solubilized (paragraph [0184]) so that the artisan would expect to solubilze the drug. However, it is also noted that an emulsion is formed in step (b) which brings us back to the point that there is more than one process sequences steps of arriving at the composition and absent factual evidence, the claimed sequence of steps is not inventive over the sequence of steps used by Unger to prepare composition comprising porous matrix where all the ingredients meeting the claimed ingredients are taught but differs in the order in which those ingredients are mixed. Therefore, Unger renders the claimed method obvious and does not teach away from the claimed method.

a3) Appellant argues that Gordon teaches away from the method described in Unger, but it is noted that Gordon is not used to reject the claims rather Gordon was cited as an evidentiary reference to show that the claimed method steps are known in the art to produce powder formulation. Gordon was not combined with Unger to reject the claims.

b) Appellant argues that Unger does not disclose or suggest adding a volatile solid pore forming agent to the drug solution and then removing the volatile pore forming agent. The examiner agrees with the appellant that Unger does not teach the exact sequence of the claimed

method steps, but the volatile solid is removed by spray drying, lyophilization and vacuum drying (paragraph [0183] and [0184]) to form microcavities

b2) Appellant says that the gas or gaseous precursors are not pore forming, but Unger specifically states that in one of the embodiments, the gaseous precursors are lithium bicarbonate, sodium bicarbonate, potassium bicarbonate, magnesium carbonate, calcium carbonate, magnesium bicarbonate, ammonium carbonate, ammonium bicarbonate, ammonium sesquecarbonate, or sodium sesquecarbonate (see paragraph [0167]) all of which meet volatile solid pore forming agents. Specifically, it is also brought to appellant's attention that claim 21 identifies ammonium carbonate as a volatile solid pore forming agent, and the ammonium carbonate is one of the gaseous precursors of Unger as stated above. A chemical compound and its properties are inseparable so that the ammonium carbonate of Unger would inherently have pore forming properties. Appellant's arguments are centered on the sequence of the appealed method steps while it is prima facie to select any order of mixing ingredients to arrive at the product. Appellant has not provided factual evidence that the appealed sequence of the method steps provides unusual results. Regarding the use of methylene chloride, a liquid, versus solid volatile agent, it is noted that because the gaseous precursors are added to the surfactant and therapeutic agent and evaporated during spray drying (paragraph [0161]) with the gaseous precursors listed in paragraph [0167], the gaseous precursors listed in paragraph [0167] meet the limitation of the volatile solid pore forming agent and contrary to appellant's assertion, paragraph [0161] does not limit the gaseous precursor to methylene chloride while disclosing that the gaseous precursors are substantially evaporated during spray drying, in fact paragraph [0167] does not list methylene chloride as one of the gaseous precursors. A chemical compound and

its properties are inseparable so that the ammonium carbonate of Unger would inherently have pore forming properties. Furthermore, it is noted that, the use of methylene chloride is another embodiment in which Unger forms porous matrix. Unger discloses other embodiments that use ammonium bicarbonate as gaseous precursor

b3) Appellant argues that Gordon does not provide the elements of what is missing in Unger, but Gordon in not used in combination with Unger to reject the claims.

c) Appellant argues that the Reply Brief filed 12/18/2007 indicated that Example 1 of Unger does not include volatile solid pore forming agent and does not disclose removing the volatile solvent and volatile solid pore forming agent from the emulsion, that PEG-Telomer B is a liquid, appellant thus says that it is unclear as to why the examiner relies on Example 1 of Unger. The examiner thanks the appellant for pointing out that Example 1 of Unger is not directed to the use of volatile solid pore formers, the examiner also acknowledges why applicant is unclear with the reference to Example 1 in the office action. However, it is noted that Unger specifically calls Example 1 prophetic and is thus not an example that the examiner relied upon. It was cited to show other processes that can/may be used in mixing ingredients for formulating compositions and not for the formation of porous matrix using volatile solid pore forming agent.

d) Appellant states that Unger does not disclose compositions containing an excipient that enhances the dissolution rate of the drug, stabilizes the drug in an amorphous form by preventing crystallization, or stabilizes the drug in crystalline form by inhibiting crystal growth. But, it is noted that enhancing the dissolution rate of the drug, stabilizing the drug in an amorphous form by preventing crystallization, or stabilizing the drug in crystalline form by inhibiting crystal growth are all derived from the function and properties of the excipient and the surfactant of

Unger meets the excipient of claim 16. Furthermore, Unger in paragraph [0019] refers to "surfactant" or "surface active agent" as substance that alters energy relationship at interfaces, such as, for example, synthetic organic compounds displaying surface activity, including, inter alia, **wetting agents**, detergents, penetrants, spreaders, dispersing agents, and **foaming agents**, hydrophobic compounds, such as include phospholipids, oils, and fluorosurfactants." Claim 18 defines wetting agents and polymers as excipients. Therefore, Unger's composition containing wetting agent contains excipient and would also intrinsically perform the recited function, which stems from the innate properties of the excipient.

e) Appellant states that the Unger does not suggest that microparticles formed by the process of Unger have the properties specified by claim 16, but since the product formed by Unger and the claimed method have the same constituents, it follows that the composition of the product formed by the claimed method and that formed by the Unger method are the same, and same compositions must have the same properties and "products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present." See MPEP 2112.01 [R-3] II. The process of Unger does not anticipate the appealed process steps but it is prima facie obvious to select any order of performing process steps in the absence of new and unexpected results. In this case, the process of Unger, though not anticipating the sequence of method steps appealed, leads to the anticipated composition comprising porous matrix. While appellant indicates that the examiner failed to address the absence of a teaching in Unger that the particles or powder have the properties recited in claim 16, it is noted that the appellant has identified

them as properties such that the composition of Unger comprising porous matrix of therapeutic agent, hydrophobic or hydrophilic excipients and particles of drug would also have the properties of TAP density that is innate to the composition except appellant factually shows otherwise that the property of the composition patentably distinguishes the appealed claims over the composition produced by Unger. The basis for expecting the properties of the appealed composition produced by the process of the appealed claims flows from the fact that same products, and in this case compositions containing particles of drug, at least one hydrophilic or hydrophobic excipient must have the same properties that are innate or intrinsic to the composition. If appellant doubts that properties are inherent to same products or compositions, the examiner takes the position that these properties are intrinsic or innate to the compositions and are inseparable from the compositions.

f) Appellant argues that unexpected or unpredictable results are used to rebut prima facie case of obviousness, but the examiner failed to establish prima facie case of obviousness, so that appealed claims 16-21 and 34 are not obvious over Unger alone or in combination with Gordon. The examiner disagrees because the process steps of Unger though not the sequence of steps of the appealed claims, combines/mixes drugs, surfactants and solvents and gaseous precursors to produce composition comprising porous matrix comprising drug and hydrophilic or hydrophobic excipients having the intrinsic properties recited in the claims, and selection of any order of mixing is prima facie obvious. The examiner made the prima facie case of obviousness. The rejection was not made over Unger in combination with Gordon.

Claim 18, Unger renders claim 18 obvious because Unger mixes therapeutic agent and surfactant to prepare the composition. Surfactant is a wetting agent (see paragraph [0019]

specifically referring to surfactant as a wetting agent). Therefore, contrary to appellant's assertion that Unger does not render the claim obvious, Unger renders the process of claim 18 where the excipient is a wetting agent.

Claims 19 and 20, Unger renders obvious claims 19 by combining therapeutic agent and surfactant to form compositions comprising porous matrix with the surfactant meeting the limitation of hydrophilic or hydrophobic excipient. Regarding the % amount of the drug, the artisan has the capability of determining how much of the drug would be needed in the composition. For example, when the therapeutic agent is anti-neoplastic agent (paragraph [0135]) a desired and suitable amount would be used that would be expected to provide the anticipated treatment such that a broad range of 1-95% of drug is met. For claim 20 that recites the presence of a volatile salt as a pore forming agent, it is noted that Unger teaches that gaseous precursors are added to the surfactant and therapeutic agent and evaporated during spray drying (paragraph [0161]) with the gaseous precursors listed in paragraph [0167], the gaseous precursors listed in paragraph [0167] meet the limitation of the volatile solid pore forming agent with potassium bicarbonate, magnesium carbonate, calcium carbonate, magnesium bicarbonate, ammonium carbonate, ammonium bicarbonate, ammonium sesquecarbonate, sodium sesquecarbonate, sodium aminomalonate and ammonium aminomalonate (paragraph [0167]), which are all volatile salts meeting the requirements of claim 20.

g) The examiner agrees with appellant's determination of who might be one having the level of ordinary skill in the art at the time the invention was made.

h) Appellant extensively discussed KSR and stated that the courts affirmed the Graham v. John Deere TSM test and as such the analysis in the rejection of the claims should have used the

TSM test. However, it is noted that while the court affirmed the TSM test, the court also said that the TSM test is not the only criteria that should be used in determining whether a claimed invention is rendered obvious by teaching of the prior art.

In the instant case, it was considered obvious to use known steps of preparing a powder with the expectation of forming porous matrix. Furthermore, changes in the sequence of adding ingredients or selection of any order of performing process steps or selection of any order of mixing ingredients is prima facie obvious (see *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1940) and I*n re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930)).

i) Appellant states that secondary considerations of the claimed invention has to do with formulating pharmaceutical compositions containing drugs having low solubility so that in consideration of the Graham analysis, the person of ordinary skill would not have been motivated to modify Unger. This is not found persuasive because, i) the generic claim 16 does not refer to low solubility drug, ii)Unger is concerned with formulating drugs such as antiviral drugs, antibiotics, anti-inflammatories (paragraph 135, right column of page 16), all of which meet the requirement of claim 34. If the classes of drugs recited in claim 34 are low solubility, then, at least the classes of drugs mentioned above and contemplated for formulation by Unger are also low solubility drugs, iii) the formulation of Unger is porous just as the claimed product formed by the claimed method, and Unger's formulation contains same excipients as that prepared by the claimed method. Therefore, the person of ordinary skill in the art would be led to formulate the low solubility drugs of Unger by the methods recognized as part of the ordinary capabilities of one skilled in the art. The selection of any order of performing process steps is

prima facie obvious in the absence of new or unexpected results; the selection of any order of mixing ingredients is prima facie obvious in the absence of new or unexpected results.

Therefore, Unger renders claims 16-21 and 34 obvious.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Blessing M. Fubara/
Examiner, Art Unit 1618

Conferees:

/Michael G. Hartley/

Supervisory Patent Examiner, Art Unit 1618

/Robert A. Wax/
Quality Assurance Specialist
Technology Center 1600